CASE REPORT

Intrastent sonotherapy in pulmonary vein restenosis: a new treatment for a recalcitrant problem

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A 2 year old boy developed recurrent pulmonary vein stenosis after surgical repair of infradiaphragmatic pulmonary venous connection. He had required implantation of stents in the left and right sided pulmonary veins at 7 and 13 months of age, respectively. By 2 years of age he had undergone three catheterisation procedures and two surgical procedures to treat recurrent pulmonary vein stenosis. His right ventricular pressure was suprasystemic and catheterisation showed severe neointimal proliferation of both left and right sided stents. At this time the stents were dilated by balloon with simultaneous intrastent sonotherapy. Three months later the patient's clinical improvement was significant, his right ventricular pressure had decreased, and Doppler velocity had decreased across both left and right sided stents.

Infradiaphragmatic obstructed pulmonary venous drainage was diagnosed in a 2 day old male infant. After surgical anastomosis of the left and right sided veins separately to the left atrium, he initially required nitric oxide for pulmonary hypertension but was extubated within five days and discharged home two weeks after surgery. He returned at 5 months of age with evidence of recurrent pulmonary venous obstruction and underwent patch enlargement of both left and right sided veins. He was referred to our institution after he developed recurrent bilateral pulmonary vein stenosis at 7 months of age. At catheterisation, the right ventricular (RV) systolic pressure was 174 mm Hg with an end diastolic pressure of 18 mm Hg and a simultaneous femoral arterial systolic pressure of 120 mm Hg and pulmonary arteriolar resistance of 31.5 Wood units. There was significant neointimal buildup in both left and right sided pulmonary veins. Two 10 mm intratherapeutic stents were implanted following a transseptal procedure increasing the diameter of the left pulmonary vein from 2 mm to 4.8 mm and the right upper pulmonary vein from 1.9 mm to 4.5 mm. The RV systolic and end diastolic pressures decreased from 174/4.16 mm Hg to 88/2.12 mm Hg and the RV to femoral arterial ratio from 1.4 to 0.9 after stent implantation.

At 13 months of age, he developed restenosis of both left and right sided pulmonary vein stents. Two additional 10 mm intratherapeutic stents were placed within the left pulmonary vein stents. The left pulmonary venous pressure decreased from 32 mm Hg to 13 mm Hg and RV systolic and end diastolic pressure decreased from 80/5 mm Hg to 65/8 mm Hg at the end of the intervention. The left sided venous stenosis increased from 2.6 mm to 6.2 mm. When he was 2 years old his clinical examination showed a prominent RV tap, a loud second heart sound, elevated jugular venous pressure, hepar span of 2 cm, and systemic oxygen saturation of 91%. He had echocardiographic evidence of systemic RV pressure by a tricuspid regurgitation jet velocity of 6 m/s. At catheterisation his RV pressure was systemic and he had severe neointimal buildup in the left sided pulmonary vein stents with a stent diameter of 7.2 mm and luminal diameter of 3.5 mm (fig 1).

After obtaining Food and Drug Administration approval and institutional approval from the ethics/internal review board of Texas Children's Hospital, we performed balloon dilatation of both left and right sided stents. A 5 French Sonotherapy catheter system (URX, Pharmasonics Inc, Sunnyvale, California, USA) was then advanced into both left and right sided stents and ultrasound was delivered at 700 Hz for 10 minutes on each side (fig 2). This resulted in significant

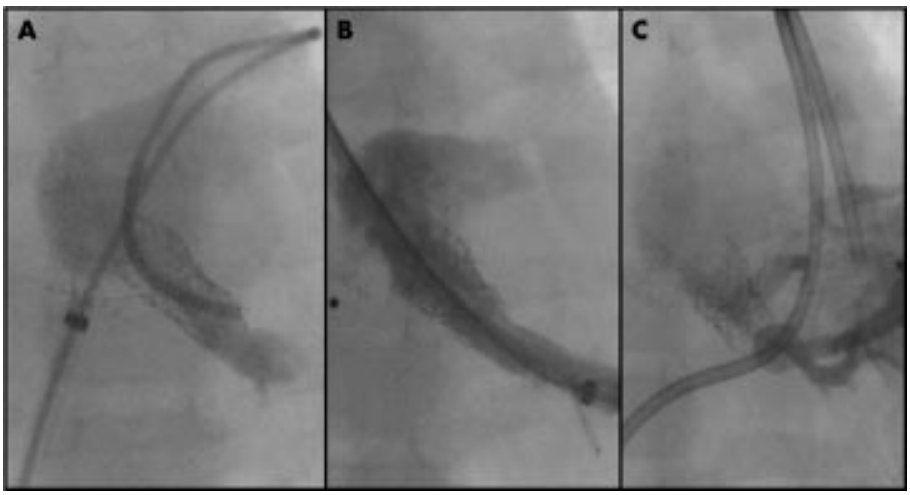

Figure 1 Left sided pulmonary vein angiogram showing (A) significant neointimal proliferation, (B) wide open stent following balloon dilatation, and (C) significant recurrence of neointimal proliferation six months later.

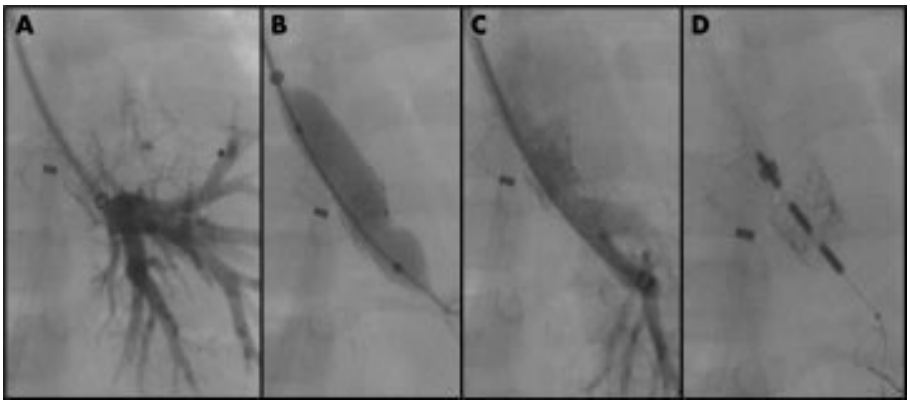

Figure 2 (A) Sheath within the stent in the left lower pulmonary vein. Contrast injection shows severe neointimal buildup with patent vessel diameter occluded by sheath. (B) Balloon dilatation of the stent. (C) Angiography following balloon dilatation. (D) Intrastent sonotherapy after balloon dilatation.

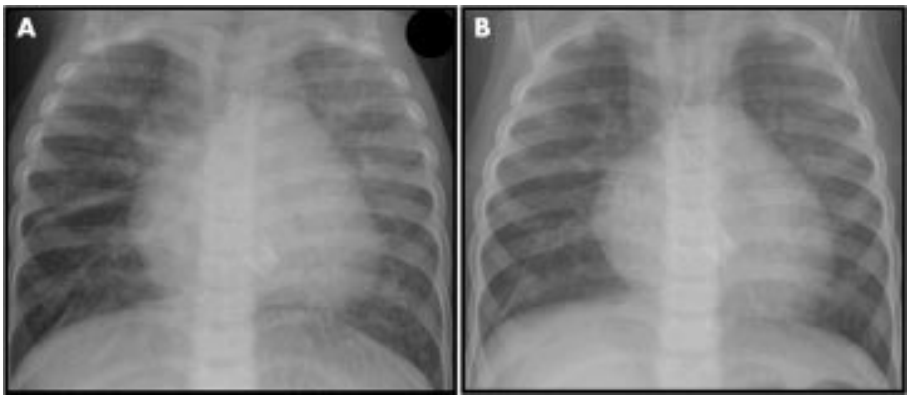

Figure 3 Chest radiograph (A) before and (B) two months after repeat balloon dilatation and intrastent sonotherapy.

resolution of the neointima with a luminal diameter of 6.7 mm on the right and 7.5 mm on the left. Precordial echocardiography one day later estimated the RV systolic pressure at 85 mm Hg by estimated tricuspid regurgitation jet velocity (4.6 m/s) with a severely dilated and hypertrophied RV and a myocardial performance index of 0.39. The peak velocity across the left pulmonary vein stent was 2.6 m/s and 1.6 m/s across the right pulmonary vein.

Three months later his parents reported that the patient had better exercise tolerance. His echocardiogram showed normalisation of interventricular septal motion, a decrease in tricuspid regurgitation to trivial, and good RV function with a myocardial performance index of 0.31. The peak velocity decreased to 2 m/s across the left sided pulmonary vein stents and 1.5 m/s across the right sided pulmonary vein stents. This was associated with an absent RV tap, normalised jugular venous pressure, and splitting of the second heart sound by physical examination. His saturation by pulse oximetry was 100% on room air at this examination. His cardiothoracic ratio decreased from 0.59 to 0.55 (fig 3).

DISCUSSION

Pulmonary venous stenosis, either congenital or postoperative, remains one of the most refractory conditions to successful surgical or interventional manipulation. Even serial implantation of stents within stenotic venous segments often fails to modify the natural course of the disease, which is invariably dismal.[1–3] Unlike arterial stenoses, neointimal proliferation and consequent restenosis within the stent are a major limiting factor in successfully palliating such stenoses. Despite minimising the potential for neointimal development by ensuring adequate stent overlap and avoiding overdilatation of the vessel greater than the luminal wall, there remains an abnormal propensity to restenosis in this group.[4]

Although this is the first report of sonotherapy in alleviating in-stent neointimal proliferation in human subjects, previous reports have described this technique in animal studies.[5 6] The rationale for using this treatment derives from the pathophysiology of neointimal growth. Initial vessel damage results in a cascade, which causes proliferation of smooth muscle cells in the media followed by their aggregation in the intima, which then accumulates extracellular matrix.[7] High intensity ultrasound results in acoustic cavitation disintegrating the smooth muscle skeleton, which in turn prevents smooth muscle cell migration.[8]

This treatment has obvious advantages over other forms of treatment previously used in coronary stents including brachytherapy and radiation therapy.[9 10] Firstly, one avoids the need for protective shielding and, secondly, there is no damage to adjacent normal vessels. Additional benefits described by Fitzgerald and colleagues[5] may stem from enhanced drug delivery or gene transfection, which may in the future be used as adjunctive treatments.

The patient reported on here has shown significant clinical, radiographic, and echocardiographic improvement three months after this new treatment, at a time when he had previously manifested clinical deterioration, increasing gradient across the pulmonary vein stents, and increasing RV pressure after prior interventions. This provides preliminary evidence that intrastent sonotherapy may be efficacious in the treatment of neointimal proliferation in pulmonary vein stenosis. Further longitudinal studies are required to assess fully its effect, in addition to determining the optimal dosage and duration of treatment required. Additional developments

in catheters of an appropriate size for children may further augment outcomes in this frustratingly refractory group of patients.

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